Remarks and Arguments

Amendments to the Claims

Claim 45 has been amended to include the feature recited in previously pending claims 46 and 48, now canceled. Claim 46 has been amended for clarity and ease of reading. Claim 47 has been amended to depend from claim 45, and has also been amended to include the feature recited in previously pending claim 48, now canceled.

Claims 49-61 have been canceled without prejudice.

Claims 62-67 have been amended to depend from claim 45.

Claims 84-90 are newly added. Support for these claims is found in Experiment 14 of the present application.

Claim 91 and 92 are newly added. Support for these claims is found in original claim 76, and throughout the specification, e.g. in paragraph [0038] of published application no. 2008-0125355 and in Experiments 6-10 and 14.

No new matter has been added as a result of the present amendments. Each of the present amendments is made without prejudice. Applicant reserves the right to pursue any subject matter canceled as a result of the present amendments in future prosecution, either in this application or in one or more continuing applications.

Sequence Listing

The paragraph beginning on page 2, lines 14 of the present specification has been amended to include reference to SEQ ID NO: 32. Applicant provides with this response a new sequence listing that includes SEQ ID NO: 32, and respectfully requests its entry into the present application. Applicant submits that the revised sequence listing comports with the requirements under 37 C.F.R. §1.821-1.825.

Foreign Priority

The Declaration was objected to for failing to identify Swedish priority application SE 0301988-2. Pursuant to 37 CFR 1.63(c)(2), an Application Data Sheet identifying this

application is submitted with this response. This rejection is therefore rendered moot, and Applicant respectfully requests its withdrawal.

"Corresponding To"

The phrase "corresponding to" in previously pending claims 45, 46, and 48 was objected to. Claims 45 and 46 have been amended to delete recitation of this phrase, and claim 48 has been canceled, rendering this objection moot.

Rejections under 35 U.S.C. §112, First Paragraph

Claims 45-50 and 62-75 were rejected under 35 U.S.C. §112, first paragraph for lack of enablement. Three separate rejections were levied, each of which is addressed below.

Central Region Sequences: Claims 45-50 and 62-75

First, the Examiner rejected claims 45-50 and 62-75, asserting that while the specification is enabling for substantially pure anti-angiogenic polypeptides consisting of SEQ ID NO: 1 or SEQ ID NO: 2, the specification does not "reasonably provide enablement for the polypeptides claimed in claims 45-50 and 62-75."

Without conceding the merits of this rejection, independent claim 45 has been amended to recite a substantially pure anti-angiogenic polypeptide consisting of SEQ ID NO: 1 or SEQ ID NO: 2. Currently amended claims 46, 47, and 62-75 depend directly or indirectly from claim 45. Moreover, newly added claim 84 recites a substantially pure anti-angiogenic polypeptide consisting of SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 27. Each of these polypeptides is enabled by the present specification (see e.g., Experiment 14).

Thus, this rejection is rendered moot, and Applicant respectfully requests its withdrawal.

In vivo Activity: Claims 66-74

Second, the Examiner rejected claims 66-74, asserting that the specification fails to demonstrate an *in vivo* activity for the claimed subfragments. The Examiner argues that "Inhibiting chemotaxis alone is insufficient to provide *in vivo* efficacy of the claimed

subfragments," and that "*In vitro* and animal model studies have not correlated well with *in vivo* clinical trial results in patients." Applicant traverses this rejection.

Without conceding the merits of this rejection, claim 45 has been amended to recite a substantially pure anti-angiogenic polypeptide consisting of SEQ ID NO: 1 or SEQ ID NO: 2. Each of claims 66-74 now depends directly or indirectly from claim 45.

It is well established that human clinical data are not necessary to establish enablement of a compound for therapeutic use. In re Brana dealt with a similar factual issue. 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the claimed compounds were anti-tumor agents. The claimed agents had been compared to structurally similar anti-tumor agents studied in earlier *in vivo* mouse studies, and had also been tested *in vitro* by determining cytotoxicity against human tumor cells. The Board of Patent Appeals and Interferences affirmed an Examiner's rejection under 35 U.S.C. §112, first paragraph for lack of enablement. Specifically, the Board found that the *in vitro* tests offered by the applicants to prove utility were inadequate" and concluded that the specification failed to prove that "the claimed compounds are useful as anti-tumor agents." In re Brana, 51 F.3d at 1566.

The Federal Circuit reversed, stating that "The Commissioner counters that such *in vivo* tests in animals are only preclinical tests to determine whether a compound is suitable for processing in the second stage of testing, by which he apparently means *in vivo* testing in humans, and therefore are not reasonably predictive of the success of the claimed compounds for treating cancer in humans. **The Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption**." Id. at 1567 (emphasis added). The Federal Circuit further explained that "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans... In view of the foregoing, we conclude that applicants' disclosure complies with the requirements of 35 U.S.C. §112, paragraph 1." Id. at 1568.

As disclosed in Experiment 6A of the present specification, "HRGP acts through the inhibition by chemotaxis of endothelial cells, which is a common feature of anti-angiogenic molecules." Experiment 6B was conducted to "determine which part of HRGP was responsible

for the anti-angiogenic effect" demonstrated in previous Experiments. Example 6B demonstrated that the His5 polypeptide, as set forth in SEQ ID NO: 2, inhibited chemotaxis of endothelial cells towards FGF-2. The polypeptide of SEQ ID NO: 2 thus exhibited a significant anti-angiogenic functional property.

Experiments 7 through 10 of the present specification deal with the Pep2 polypeptide fragment as set forth in SEQ ID NO: 1. Collectively, these Experiments demonstrate the Pep2 polypeptide also exhibits anti-angiogenic effects. Indeed, in Experiment 10 the Pep2 polypeptide was compared to full-length HRGP for its effect on tumor size reduction in female mice. Figure 8 shows that animals injected with either full-length HRGP or the Pep2 polypeptide exhibited smaller tumors than control animals.

Moreover, Experiment 14 demonstrates that the polypeptides recited in newly added claims 85-90 exhibit *in vitro* inhibitory effect on chemotaxis (see e.g., Table 2). For reference, Pep 9A is the sequence of SEQ ID NO: 16, Pep 10 is the sequence of SEQ ID NO 18:, Pep 12A is the sequence of SEQ ID NO: 21, Pep 13A is the sequence of SEQ ID NO: 23, and Pep 15A is the sequence of SEQ ID NO: 27. As such, the polypeptides of SEQ ID NO's: 16, 18, 21, 23 and 27 exhibited a significant anti-angiogenic functional property.

Thus, one of ordinary skill in the art would understand upon reading the present specification that the polypeptides of SEQ ID NO's: 1, 2, 16, 18, 21, 23 and 27 exhibit anti-angiogenic properties. Moreover, one of ordinary skill in the art would be able to make and use these polypeptides without undue experimentation, including making and using pharmaceutical composition comprising an effective amount of the polypeptides, as recited in claims 66-74 and 90.

Applicant thus respectfully requests that this rejection be withdrawn.

Zn2+: Claim 75

Third, the Examiner rejected claim 75, asserting that SEQ ID NO: 1 lacks the metal-binding domain, and that it is thus not clear how the claimed Zn2+ would act as a cofactor. Applicant traverses this rejection.

Claim 75 depends indirectly from claim 45. Claim 45 has been amended to recite a substantially pure anti-angiogenic polypeptide consisting of SEQ ID NO: 1 or SEQ ID NO: 2.

Both SEQ ID NO's: 1 and 2 contain histidine-rich regions, and both include the amino acid sequence GHHPH, a motif involved in Zinc binding. As such, each of SEQ ID NO's: 1 and 2 would be expected to coordinate Zinc.

Moreover, as described above, the Pep2 polypeptide (SEQ ID NO: 2), which contains only a single GHHPH motif, was shown to exhibit anti-angiogenic effects while being administered in conjunction with Zinc. In Experiment 10, female mice received either full-length HRGP or the Pep2 polypeptide, both of which were administered in conjunction with Zn acetate. As shown in Figure 8, animals injected with either full-length HRGP or Pep2 exhibited smaller tumors than control animals. Thus, these data show that the Pep2 polypeptide was shown to function like full-length HRGP in the tumor size assay, and did so while being administered with Zn2+, as recited in claim 75.

Applicant thus respectfully requests that this rejection be withdrawn.

Rejections under 35 U.S.C. §102

Koide et al.

Claims 45, 47, 49-50, and 62-66 were rejected under 35 U.S.C. §102(b) as being anticipated by Koide *et al.*, Biochemistry 25:2220, 1986 ("Koide *et al.*"). Previously pending independent claim 47 has been canceled. Independent claim 45 has been amended to include the features recited in previously pending claims 46 and 48, respectively. Thus, this rejection is rendered moot, and Applicant respectfully requests its withdrawal.

WO 02/076486

Claims 45-51 and 62-74 were rejected under 35 U.S.C. §102(b)/(e) as being anticipated by PCT publication WO 02/076486, corresponding to US 2005-0042201. Without conceding the merits of this rejection, independent claim 45 has been amended to recite a substantially pure anti-angiogenic polypeptide consisting of SEQ ID NO: 1 or SEQ ID NO: 2.

The Examiner notes that WO 02/076486 refers to amino acid residues 330-439 of HRGP as the "his/pro region." In contrast, the present specification refers to amino acids 240-390 of mature human HRGP as SEQ ID NO: 2, and amino acids 330-364 of mature human HRGP as

SEQ ID NO: 1. WO 02/076486 does not teach an anti-angiogenic polypeptide consisting of either SEQ ID NO: 1 or SEQ ID NO: 2, as recited in currently amended claim 45.

Thus, this rejection is rendered moot, and Applicant respectfully requests its withdrawal.

WO 02/064621

Claims 47, 49-50, and 62-65 were rejected under 35 U.S.C. §102(b) as being anticipated by PCT publication WO 02/064621. Previously pending independent claim 47 has been canceled. Independent claim 45 has been amended to include the features recited in previously pending claim 48. Thus, this rejection is rendered moot, and Applicant respectfully requests its withdrawal.

US Pat. No. 7,294,515

Claims 47, 49-50, and 62-68 were rejected under 35 U.S.C. §102(e) as being anticipated by US Pat. No. 7,294,515. Previously pending independent claim 47 has been canceled. Independent claim 45 has been amended to include the features recited in previously pending claim 48. Thus, this rejection is rendered moot, and Applicant respectfully requests its withdrawal.

In light of the present amendments and remarks, Applicant submits that the present application is in condition for allowance, and respectfully requests a notice to that effect. If the Examiner feels that it would further prosecution or expedite allowance of the present case, he is invited to telephone the undersigned at 612-766-2071.

Please charge the required Extension of Time fee of $245 and any other charges, and credit any overpayments, to deposit account 06-1050, referencing Attorney Docket No. 15665-0007US1.

Respectfully submitted,

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